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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/163,272	09/29/1998	JONATHAN DINSMORE	DNI-041CPA	9801

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/163,272	DINSMORE, JONATHAN	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-18,20-26 and 28-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-18,20-26 and 28-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/03 and 06/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed May 24, 2004 (hereinafter referred to as "the response") has been entered. Claims 49-64 have been newly added.

Accordingly, Claims 1, 3-8, 10-18, 20-26, and 28-48 remain pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on May 24, 2004 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1, 3-8, 10-18, 20-26, and 28-48 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 3-9 of the Office Action of Paper No. 6 (mailed 12/7/99), on pages 2-3 of the Office Action of Paper No. 11 (mailed 10/18/00), on pages 2-3 of the Office Action of Paper No. 14 (mailed 7/3/01), on pages 2-4 of the Office Action of Paper No. 25 (mailed 7/16/02), and on pages 2-5 of the Office Action mailed 4/24/03, because the

specification, while being enabling for a method of treating a xenogeneic subject having spinal cord damage arising from amyotrophic lateral sclerosis or spinal cord injury, does not reasonably provide enablement for treating a xenogeneic subject having spinal cord damage arising from the claim-designated neurodegenerative disorders or aging. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 3-8, 10-17, 38-42, 45, 47, and 48 are directed to compositions. However, the claims recite an intended use. As such the specification must provide an enabling disclosure for the intended use. Moreover, the intended use must be enabled for its full scope.

The specification fails to provide an enabling disclosure for the method of cell-based therapy because methods of xenotransplantation of neural tissue are not routinely successful and the specification does not offer adequate specific guidance to enable one skilled in the art to practice the claimed invention over the full scope to derive a therapeutic benefit in an immunocompetent diseased animal. The art demonstrates that methods of xenotransplantation of neural tissue is unpredictable due to the immune response of the host, which leads to graft rejection if adequate immunosuppression cannot be achieved. Brevig et al. (2000) teaches that "in animal models, neural tissue transplanted between species is usually promptly rejected, even when implanted in the brain. Some of the immunological mechanisms that underlie neural xenograft rejection have recently been elucidated, but others remain to be determined and controlled before individuals with neurological disorders can benefit from xenotransplantation" (see abstract). The reference further teaches that "[c]yclosporin, an immunosuppressant that effectively inhibits T-cell alloreactivity, is inadequate at protecting neural xenografts from immune attact in rats" (p. 341, column 2, paragraph 3) and that an "individual with Parkinson's disease who received porcine embryonic VM grafts about eight months earlier almost completely rejected his grafts, as determined by histology at autopsy" (p. 342, column 1, paragraph 1). The

authors suggest that immunosuppression must be more aggressive "or supplemented with another strategy that inhibits or prevents the host T-cell response" (p. 342, column 1, paragraph 1). Although the instant specification suggests masking MHC class-I antigens, there is no teaching that this additional treatment of the donor tissue is sufficient to prevent graft rejection. Brevig et al. discuss the trial in Parkinson's patients where porcine embryonic cells were transplanted and points out that graft survival was poor and T cell infiltration was observed in the one subject that underwent autopsy. The authors state "[t]he two stategies to reduce T-cell mediated rejection, masking of MHC class-I antigens and treatment with cyclosporin, were known to be inadequate in the pig-to-rat model. This initial trial has shown that these strategies are also inadequate in humans" (p. 343, column 1, paragraph 1).

Armstrong et al. (2001) provide a detailed discussion of rejection mechanisms for porcine neural xenografts in the immunocompetent rat. In addition to the T cell response, the reference also discusses the humoral response and points out that "[t]he blood-brain barrier (BBB) is normally an effective barrier to the passage of immunoglobulins ... but is compromised by the necessary trauma of the grafting procedure thus allowing transient acess of systemically produced antibodies" (p. 213, column 1, paragraph 2). Armstrong et al. detected IgM in rejecting grafts at all time points and therefore point out that the BBB may be compromised for extended periods (p. 213, bottom of colum 1 to top of column 2).

Larsson et al. (2000) report some functional recovery in rats xenografted with porcine embryonic ventral mesencephalic tissue, but point out that graft rejection remains as a significant issue and that more effective immunosuppressive drug treatments are needed.. The reference reports that "[i]mmunosuppressive treatment was necessary for long-term graft survival and functional recovery, but did not sufficiently protect from rejection mechanisms" (see abstract).

Rowe (1996) and Dorling et al. (1997) provide additional discussion of the challenges of xenotransplantation just prior to the effective filing date of the instant application, particularly

with regard to hyperacute rejection (HAR) and the further barriers that might exist to limit the survival of xenografts beyond the HAR phase (see abstract of Dorling et al.).

The Declaration of Dr. Dinsmore has been fully considered but has not been found persuasive because the description of the transplantation procedure is incomplete and therefore it is impossible to know if the transplantations were carried out in accordance with the teachings of the specification.

Given the lack of specific guidance in the specification directed to the wide variety of disorders recited in the claims, the broad scope of the claims, and the limited working examples directed to producing a therapeutic effect upon transplantation of porcine spinal cord cells into an animal model of ALS and an animal model of spinal cord injury, one of skill in the art would have been required to engage in undue experimentation to practice the claimed method over the full scope and use the claimed compositions for their intended use, over the full scope.

At pages 13-15 of the response, Applicants point to the Declaration of Dr. Dinsmore filed January 21, 2003. This Declaration and the results presented therein have already been addressed in the Office Action mailed April 24, 2003, as reiterated herein above. Applicants further provide and point to a protocol sheet which was provided to physicians performing the xenogeneic transplantations. Applicants argue that the protocol sheet shows that the protocol is in accordance with the teachings of the specification. However, no evidence has been offered to support that the protocol described on the protocol sheet corresponds to the protocol that was used to produce the results referred to in the Declaration of Dr. Dinsmore. Attorney argument cannot substitute for actual evidence. Furthermore, the protocol sheet clearly constitutes guidance, recommendations, or direction, but does not disclose the details of how the transplantations were actually carried out. It does not disclose the actual number of cells injected, the actual number of injection sites, whether the patient was immunosuppressed, how the immunosuppression was carried out, or

whether the cells were treated to decrease their immunogenicity. Thus, it is impossible to know if the transplantations were carried out in accordance with the teachings of the specification.

At pages 15-17 of the response, Applicants dismiss the various references cited in the enablement rejection as not pertaining to the instant invention. At page 15 of the response, in the last sentence, Applicants assert that the issues discussed in Brevig are specific to xenotransplantations relating to the brain and are contradictory to the data presented by the specification as well as the data presented in the previous Declaration. For the reasons discussed above, it is noted that the data presented does not provide information regarding methodology for preventing xenograft rejection, nor does it positively state that no immunosuppression was used or that the cells were not subjected to a treatment to decrease their immunogenicity. The Declaration is silent with regard to this issue. Furthermore, the issues discussed in Brevig do not apply only to xenotransplantation to the brain, but rather are presented as relating to the central nervous system (CNS). The CNS includes the spinal cord.

At page 16, paragraph 3 of the response, Applicants argue that the Armstrong reference provides some suggestions for reducing the immunogenicity of the transplanted cells. However, the Armstrong reference, as well as the other references cited, are in agreement that methods for reducing immunogenicity are inadequate for xenotransplantation to humans. Thus, the references individually and in combination when viewed as a whole, clearly support the notion that xenotransplantation and the clinical effects resulting therefrom are highly unpredictable due to inadequate immunosuppression and the resulting graft rejection.

At page 17, paragraph 2 of the response, Applicants again rely on the "results provided in the Declaration" and argue that said results provide evidence that efforts can be taken to immunosuppress the recipient or reduce the immunogenicity of the cells being transplanted. It is again noted, however, that the Declaration does not provide any information with regard to steps actually taken to overcome the art-recognized problem of graft rejection.

Conclusion

Claims 49-64 are allowable in view of the examples set forth in the specification.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the

problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER